meaning that is understood in the art, and that one of ordinary skill in the art would understand the common meanings of these terms as they are used in the art. Further, Applicants teachings in the specification would apprise one of ordinary skill in the art of the scope of the claims. See, for example, page 8 and the teachings of the detailed description beginning on page 13.

Claim 1 is rejected as the term "administration" is deemed indefinite. Applicants respectfully direct the examiner's attention to pages 22-24 of the Specification as filed. In these pages of the specification, Applicants have fully defined the meaning of the term "administration" and have distinctly pointed out that heparinase enzymes can be administered either locally or systemically and that the means administration can be injection, infusion or perfusion.

Claims 1-7 are rejected as the term "heparinase enzyme" is deemed indefinite. Applicants respectfully direct the Examiner's attention to page 8, lines 11-17, wherein Applicants define the term "heparinase enzyme" to include: heparinases I, II, and III from the Gram negative bacterium *Flavobacterium heparinum*, heparinase from *Bacteriodes* strains, heparinase from *Flavobacterium* Hp206, heparinase from *Cytophagia* species and heparanases from mammalian cells.

In view of the remarks above, Applicants respectfully submit that claims 1-7 are definite. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

2. Claims 1-7 are enabled under 35 USC §112, first paragraph.

Claims 1-7 were rejected as lacking enablement. In the Office Action at paragraph 11, the Examiner agrees that the specification enables a method to decrease inflammatory response in ischemic tissue, however, the Examiner also states that the specification "does not reasonably provide enablement for numerous inflammatory diseases or conditions disclosed on page 1, lines 25-35". The Examiner provides support for this position through reasoning that use of therapeutic proteins is unpredictable due to problems with stability and delivery. This rejection is respectfully traversed.

As a preliminary matter, Applicants respectfully clarify that page 1, lines 25-35, describe a list of harmful inflammatory responses that can occur following an ischemia/reperfusion injury to tissue. With respect to, for example, allograft rejection, Applicants are not claiming a treatment for allograft rejection per se. Instead, Applicants are claiming a method to decrease the localized inflammatory response in a tissue following an ischemic/reperfusion injury, one example of which is tissue injury that arises as a result of allograft rejection.

Although the therapeutic usefulness of many proteins is unknown, Applicants have demonstrated the therapeutic usefulness of heparinase enzymes according to the claimed invention through *in vivo* studies. Applicants have shown that heparinase enzymes can be administered systemically by infusion to achieve a steady plasma concentration of heparinase enzyme. Following ischemia/reperfusion (which would be caused by events such as heart attack, stroke, or surgery) the heparinase enzymes were demonstrated to be active and to decrease the localized inflammatory response. (See, for example, specification pages 35-45). Thus, Applicants have demonstrated

that active heparinase enzymes can be delivered to a patient to decrease the localized inflammatory response.

Applicants respectfully submit that the claimed invention is fully enabled by the teachings of the specification. The Examiner is requested to reconsider and withdraw this rejection.

3. The claims are novel under 35 USC § 102 in view of the cited art.

Claims 1-7 were rejected under 35 USC §102(a) in view of Lider et al. This rejection is respectfully traversed.

Applicants respectfully point out that delayed type hypersensitivity (DTH) is a cell mediated immune response, i.e. allergic response, which occurs in immune individuals. DTH is not an "inflammatory response" and is not within the definition of that term as defined in the specification at page 1, lines 16-28.

Further, contrary to the statements in the Office Action at paragraph 15.A, Lider et al does **not** teach a method to decrease localized inflammatory response by administering heparanase, nor does Lider et al. teach that heparanase inhibits secretion of TNF-α. Rather, Lider et al. teaches that the administration to mice of a purified disaccharide product of the extracellular matrix (ECM) in particular concentrations results in a decrease in the DTH reaction and inhibits secretion of active TNF-α. In fact, insofar as the Examiner considers DTH to be an inflammatory response, Lider et al. teaches away from Applicants' claimed invention through the teaching that the natural product of heparanase digestion of the ECM, the unpurified material, does not inhibit DTH reactivity. Therefore, Lider et al. does not identically teach that which Applicants' claim in claims 1-7 and cannot anticipate claims 1-7.

Reconsideration and withdrawal of this rejection is respectfully requested.

4. The claims are patentable under 35 USC § 103 in view of the cited art.

Claims 1-7 were rejected under 35 USC §103(a) as being unpatentable over Hoogewerf et al., Gilat et al. (J. Exp. Med.), Vlodavsky et al., Lider et al., Zimmerman et al. (USPN 5,169,772), Fuks et al. (USPN 5,362,641), and Sasisekharan et al. (5,567,417) in view of Ratner et al. or Gilat et al. (J. Immunol.). Applicants respectfully traverse this rejection.

The claimed invention is based on the unexpected discovery that administration of heparinase enzyme to a patient decreases the localized inflammatory response. Applicants are not claiming a composition comprising heparinase enzymes. Applicants are claiming an new and unexpected use for heparinase enzymes. As the discoverers of a new use for these compounds, based on an unknown property, Applicants are entitled to claim a method for using these compounds.

Contrary to the statements in the Office Action, none of the cited art, either separately or taken together teaches or *fairly* suggests the administration of heparinase enzyme to decrease a localized inflammatory response.

More specifically, as noted by the Examiner, none of Hoogewerf et al, Gilat et al. (J. Exp. Med.), Vlodavsky et al, and the '772 Patent teach or suggest the use of heparinase enzymes to decrease a localized inflammatory response. The '641 patent suggests that administration of heparanase leads to a mobilization of fibroblast growth factor (FGF) which may be useful to promote wound healing and neovascularization, and to treat disease conditions which are likely to benefit from neovascularization promoted by FGF. See, col 4, lines 55-57 and col. 4, line 66 through col. 5, line 6. The '417 patent teaches that administration of heparanase

alone can inhibit neovascularization, and suggests that administration of heparanase may be useful in treatment of disease states which depend upon neovascularization. As discussed above, Lider et al. teaches that the administration of a purified ECM disaccharide inhibits the DTH response but does not teach or suggest administration of heparanase enzyme. Therefore, none of the primary references teach or suggest that administration of heparinase to decrease a localized inflammatory response.

In addition, the secondary references of Gilat et al. (J. Immunol.) and Ratner et al. do not provide that which the primary references lack. Ratner et al. provides no teaching or suggestion that administration of a heparinase enzyme to a patient would decrease a localized inflammatory response. Gilat et al. (J. Immunol.) suggests that degradation of the extracellular matrix by heparanase enzymes would result in the release of chemokines and the subsequent mobility of leukocytes which would then migrate to sites of inflammation. The result of such migration of leukocytes would be a localized inflammatory response. Thus, Gilat et al. teaches away from Applicants claimed invention of administering heparinase enzymes to decrease a localized inflammatory response.

Based on the foregoing remarks, the examiner is respectfully requested to reconsider and withdraw this rejection of claims 1-7.

5. Obviousness-Type Double Patenting.

Claims 1-7 were provisionally rejected under the judicially created doctrine of obvious-type double patenting over claims 1-10 of copending Application No. 08/273,109.

Applicants' respectfully request that this rejection to the claims be held in abeyance until allowable subject matter is indicated in both the instant application and in Application No. 08/273,109.

Summary

Entry of the present amendments and reconsideration of the amended application, in view of the foregoing remarks, are respectfully requested. The amended application should be in condition for allowance, and such action is respectfully requested. If the Examiner believes that a telephone conversation would expedite prosecution in this Application, the Examiner is invited to telephone the undersigned at (617) 526-6460.

If there are any additional payments due or credits owed, please make them to our Deposit Account No. 08-0219.

Respectfully submitted,
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